REMARKS

This amendment is in response to the Advisory Action of March 16, 2001 in which the Examiner stated that the previous response was not entered as the claim amendments did not comply with the formal requirements of 37 C.F.R. 1.121(a)(2)(i). Accordingly, Applicant is re-submitting the previous response in proper format.

Claims 2, 6-12 and 39, and 43-55 are pending in the present application. Claims 2 and 39 have been amended to recite that the respiratory dispersion comprises a plurality of perforated microstructures that are substantially permeated by the suspension medium wherein the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure. Support for this amendment is found throughout the specification, for example at page 17, line 23 – page 18, line 11. Withdrawn claims 13-38 have been canceled while Applicant reserves the right to pursue them in one or more divisional filings. Applicant respectfully submits that no new matter is introduced by this amendment, nor does the present amendment require new consideration by the Examiner. Entry thereof is respectfully requested.

Claims 2 and 39 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter not described in the specification. Although Applicant does not agree with this rejection, in order to expedite prosecution of this application. Claims 2 and 39 have been amended to recite language which finds explicit support in the specification, for example at page 18, lines 1-3. The claims as amended now recite that the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure. Applicant respectfully submits that this rejection should be withdrawn.

The test under 35 U.S.C. 101 for whether a specification supports claim language does not require explicit disclosure of the claim language in the specification, but rather what the specification reasonably conveys to one of ordinary skill in the art. The specification at page 17, last line – page 18, line 3 states the following: "Preferably, the average volume of the bioactive agent and/or excipient shell or matrix (i.e. the volume of medium actually displaced by the perforated microstructure) comprises less than 70% of the average particle volume (or less than 70% of the virtual particle)." Another way of describing this limitation is that more than 30% of

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the average particle volume of the perforated microstructures is permeated by said suspension medium. Thus, the present amendment does not alter the scope of the claims in any manner and is merely being made to expedite prosecution.

Claims 2, 6-12, 39, and 43-55 have been rejected under 35 U.S.C. § 103 as being unpatentable over Faithfull et al. in view of Hanes et al. As discussed above, claims 2 and 39 have been amended to recite that the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure. Such a limitation to the claims was presented in Applicant's previous response as set forth above. However, it is not clear from the Final Office Action whether the Examiner considered these limitations in maintaining the 103 rejection, as the rejection and the Examiner's Response to Arguments are absolutely silent as to any mention of this limitation.

Applicant respectfully submits that the rejection should be withdrawn for the reasons that follow. Such shell volumes as defined by the present claims typically contribute little to the virtual particle density, which is overwhelmingly dictated by the suspension medium found therein. This control of particle morphology according to the present invention provides a unique solution to problems associated with providing stable suspensions for pulmonary delivery.

Faithfull et al. is directed to an apparatus and method for closed circuit ventilation therapy. As disclosed at column 16, lines 27-55, the ventilation system may further comprise a nebulizer 98 communicating with the inspiratory ventilating conduit 50. The nebulizer may be used to deliver liquid medium such as fluorochemicals heated above body temperature to the ventilating gas in the form of a vapor to assist in gas exchange and oxygenation. As seen at column 17, lines 5-29, Faithfull et al. teaches performing partial liquid ventilation (PLV) comprising the administration of very low doses of fluorochemicals (0.01 ml/kg or less) sufficient to form a thin coating on a portion of the lung to reduce surface tension at the alveolar air-liquid interface thereby facilitating lung expansion and increasing oxygen availability. Alternatively, Faithfull et al. suggests the use of a nebulizer to administer fluorochemical or respiratory agents to the gas flow path for the closed-circuit ventilation system (22: 26-35, 23: 35-42).

However, Faithfull et al. is silent as to stability problems associated with suspensions for nebulization. Thus, Faithfull et al. in no way discloses or suggests the unique approach of the

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claimed invention wherein particle morphology of perforated microstructures is controlled in order to provide stable suspensions in a fluorochemical medium for nebulization. Specifically, Faithfull et al. does not disclose or suggest a plurality of perforated microstructures comprising at least one bioactive agent suspended in and substantially permeated by a fluorochemical continuous phase wherein the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure as claimed by Applicant.

Hanes et al. does not satisfy these deficiencies of Faithfull et al. Although Hanes et al. is directed to porous particles for aerosol drug delivery, the disclosure therein is silent as to the use of fluorochemicals as a suspension medium as well as problems associated with particle suspensions for aerosol delivery and suspension stability in such a suspension medium. The particles disclosed in Hanes et al. are directed to aerosol delivery as a dry powder. The rough surface texture to reduce particle aggregation and improve flowability of the powder as cited in Hanes 4:53-56 relates to properties and characteristics of dry powders administered as aerosols. Such properties are not related to stability of the dry powder in a liquid suspension medium.

With no recognition of the problem addressed by the present invention, Hanes et al. provides absolutely no guidance to one of ordinary skill in the art seeking to address problems related to suspension stability. In particular, Hanes et al. does not disclose or suggest a plurality of perforated microstructures comprising at least one bioactive agent suspended in and substantially permeated by a fluorochemical continuous phase wherein the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure as claimed by Applicant. Thus, Applicant respectfully submits that the rejection of claims 2, 6-12 and 39, and 43-55 has been overcome and should be withdrawn.

CONCLUSION

Applicants believe that all the pending claims are presently in condition for allowance.

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However, the Examiner is invited to telephone the undersigned attorney at the number below if it is believed that this will expedite prosecution of the present application.

Respectfully submitted,

Dated: 3/23/01

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

(Twice amended) A method for the pulmonary delivery of one or more bioactive agents comprising the steps of:

providing a stabilized respiratory dispersion comprising one or more bioactive agents wherein the respiratory dispersion comprises a plurality of perforated microstructures suspended in and substantially permeated by a fluorochemical continuous phase wherein [more than 30%] the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure[s is permeated by said suspension medium];

nebulizing said respiratory dispersion with a nebulizer to provide an aerosolized medicament; and

administering a therapeutically effective amount of said aerosolized medicament to at least a portion of the pulmonary passages of a patient in need thereof.

Claims 13-38 have been cancelled.

39. (Twice amended) An inhalation system for the pulmonary administration of a bioactive agent to a patient comprising:

a fluid reservoir;

a stable respiratory dispersion in said fluid reservoir wherein said stabilized dispersion comprises a fluorochemical continuous phase and a plurality of perforated microstructures comprising at least one bioactive agent suspended in and substantially permeated by the continuous phase wherein [more than 30% of the average particle] the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure[s is permeated by said suspension medium]; and

a nebulizer operably associated with said fluid reservoir wherein the nebulizer is capable of aerosolizing and discharging the stable respiratory dispersion.

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PENDING CLAIMS

2. A method for the pulmonary delivery of one or more bioactive agents comprising the steps of:

providing a stabilized respiratory dispersion comprising one or more bioactive agents wherein the respiratory dispersion comprises a plurality of perforated microstructures suspended in and substantially permeated by a fluorochemical continuous phase wherein the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure;

nebulizing said respiratory dispersion with a nebulizer to provide an aerosolized medicament; and

administering a therapeutically effective amount of said aerosolized medicament to at least a portion of the pulmonary passages of a patient in need thereof.

6. The method of claim 2 wherein the mean aerodynamic diameter of the perforated microstructures is between 0.5 and 5μm.

7. The method of claim 2 wherein said perforated microstructures comprise a surfactant.

8. The method of claim 7 wherein said surfactant is selected from the group consisting of phospholipids, nonionic detergents, nonionic-block copolymers, ionic surfactants, biocompatible fluorinated surfactants and combinations thereof.

9. The method of claim 7 wherein said surfactant is a phospholipid.

10. The method of claim 9 wherein said phospholipid is selected from the group consisting of dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, behenoylphosphatidylcholine, arachidoylphosphatidylcholine and combinations thereof.

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11. The method of claim 2 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary lung surfactants, analgesics, antibiotics, leukotriene inhibitors or antagonists, antihistamines, antiinflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

12. The method of claim 2 wherein said bioactive agent is delivered to the systemic circulation of said patient.

39. An inhalation system for the pulmonary administration of a bioactive agent to a patient comprising:

a fluid reservoir;

a stable respiratory dispersion in said fluid reservoir wherein said stabilized dispersion comprises a fluorochemical continuous phase and a plurality of perforated microstructures comprising at least one bioactive agent suspended in and substantially permeated by the continuous phase wherein the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure; and

a nebulizer operably associated with said fluid reservoir wherein the nebulizer is capable of aerosolizing and discharging the stable respiratory dispersion.

43. The system of claim 39 wherein said perforated microstructures comprise a surfactant.

44. The system of claim 43 wherein said surfactant is selected from the group consisting of phospholipids, nonionic detergents, nonionic block copolymers, ionic surfactants, biocompatible fluorinated surfactants and combinations thereof.

45. The system of claim 43 wherein said surfactant is a phospholipid.

46. The system of claim 45 wherein said phospholipid is selected from the group consisting of dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine,

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disteroylphosphatidylcholine, behenoylphosphatidylcholine, arachidoylphosphatidylcholine and combinations thereof.

47. The system of claim 39 wherein the mean aerodynamic diameter of the perforated microstructures is between 0.5 and 5μm.

48. The system of claim 39 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary lung surfactants, analgesics, antibiotics, antiinfectives, leukotriene inhibitors or antagonists, antihistamine, antiinflammatories, antineoplastics, antocholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzyme, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

49. The system of claim 39 wherein said bioactive agent comprises a compound selected from the group consisting of proteins, peptides and genetic material.

50. The system of claim 39 wherein said fluid reservoir is a multi-dose reservoir or a single dose reservoir.

51. The system of claim 39 wherein said nebulizer is a jet nebulizer, an ultrasonic nebulizer or a single-bolus nebulizer.

52. The system of claim 39 wherein the respiratory dispersion comprises a creaming time of greater than 1 minute.

53. The system of claim 39 wherein the respiratory dispersion comprises a creaming time of greater than 30 minutes.

54. The system of claim 39 wherein the perforated microstructures comprise a geometric diameter of 1-30μm.

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55. The system of claim 48 wherein the bioactive agent is an antiinfective selected from the group consisting of cephalosporines, macrolides, quinoline, penicillins, streptomycin, sulphonamides, tetracyclines, and pentamidine.

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